

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
25 March 2004 (25.03.2004)

PCT

(10) International Publication Number
WO 2004/024123 A1

(51) International Patent Classification⁷: A61K 9/127, 31/683, 9/16, A61P 37/00

(21) International Application Number: PCT/CA2003/001407

(22) International Filing Date: 15 September 2003 (15.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/411,314 16 September 2002 (16.09.2002) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



A1

WO 2004/024123 A1

(54) Title: ACCELERATING RECOVERY FROM TRAUMA

(57) **Abstract:** Mammalian patients suffering from physical trauma, or about to likely suffer such trauma (by surgical treatment, or by suffering unanticipated accidental injuries, battle injuries or the like) are treated to lessen the severity of or accelerate the recovery from such consequently sustained trauma, by administering to the patient immune system-modifying entities, each comprising a body of a size similar to an apoptotic mammalian cell or apoptotic body, and having exposed on its surface phospho-glycerol groups, the entities being capable of being taken up by cells of the patient's immune system with accompanying beneficial effects including inhibition of pro-inflammatory cytokines and/or promotion of anti-inflammatory cytokines. The entities may be phosphatidylglycerol-presenting liposomes, generally of size 50 nanometers to 500 microns, and administered to contact a patient's immune system (e.g. intramuscularly) in amounts which affect but do not overwhelm the patient's immune system.

ACCELERATING RECOVERY FROM TRAUMA

FIELD OF THE INVENTION

This invention relates to therapeutic compositions and uses thereof in medical treatments and prophylaxis to lessen the effects of adverse medical conditions. More specifically, it relates to acceleration of recovery of a patient from the physical trauma of surgery and other wounds and injury conditions, and to methods of pre-conditioning the mammalian body so as better to withstand such physical trauma.

BACKGROUND OF THE INVENTION

There is a continuing need to shorten the hospital stay of patients undergoing surgical procedures or treatment for physical trauma, which effectively means accelerating the rate of recovery of a patient from the trauma of surgery or other injuries. This applies both to patients undergoing pre-scheduled or elective surgery, to patients undergoing surgery as a result of accidental injury or treatment of an unforeseen medical emergency and to patients recovering from physical trauma having an inflammatory component. There is also a continuing need to better treat patients who suffer from myocardial infarction. Both for the comfort and rapid recovery of the patient, and for the benefit of health care economics, it is desirable to be able to accelerate the rate of recovery of a patient from such trauma.

It would also be desirable to be able to pre-condition a patient scheduled to undergo surgery, so that the patient would be better able to withstand the trauma associated with surgery, to lead to a more rapid recovery from trauma afterwards. It would also be advantageous to be able to precondition persons at risk of sustaining injury (battle troops, rescue personnel and the like) to enable them to recover more rapidly from such trauma.

SUMMARY OF THE INVENTION

The present invention is based upon the novel appreciation of the role played by the up-regulation of anti-inflammatory cytokines and/or the down regulation of inflammatory cytokines in a patient's body, and by improved endothelial function, on the mammalian body's wound process of recovery from physical trauma such as from surgery and other wounds. The natural process of apoptosis (programmed cell death) leads to the upregulation of anti-inflammatory cytokines and the down-regulation of inflammatory cytokines in the mammalian body, as well as improvements in endothelial function. The present invention provides a process of accelerating the recovery of a patient from physical trauma (surgical or accidental), and a process of pre-conditioning to accelerate the recovery from subsequently experienced such trauma, which mimics the apoptosis process of the mammalian body and takes advantage of the beneficial effects flowing from apoptosis *in vivo*, to effect such processes.

According to one aspect of the present invention, there is provided for use in the preparation of a medicament for treating a mammalian patient suffering from physical trauma, or treating a mammalian patient at risk of suffering such trauma (by surgical treatment, or by suffering unanticipated accidental injuries, battle injuries or the like) to lessen the severity of and/or accelerate the recovery from such trauma, of an effective immune system modifying amount of immune system-modifying entities, each comprising a body of a size similar to an apoptotic mammalian cell or apoptotic body, and having exposed on its surface phospho-glycerol groups, the entities being capable of modulating the patient's immune system with accompanying beneficial effects including inhibition of pro-inflammatory cytokines and/or promotion of anti-inflammatory cytokines.

THE PREFERRED EMBODIMENTS

One preferred category of such entities, the use of which in treatment of trauma and preconditioning against trauma constitutes a preferred embodiment of the present invention, is biocompatible synthetic entities such as biocompatible beads, comprising:

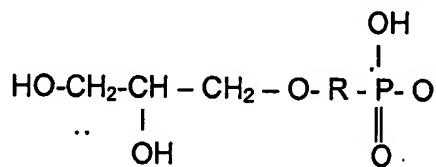
a three-dimensional head portion of size in its largest dimension of from 50 nanometers to 500 microns;

a plurality of tail portions bonded to each said head portion, the tail portions having:

phospho-glycerol end groups capable of modulating the appropriate receptors on antigen-presenting cells,

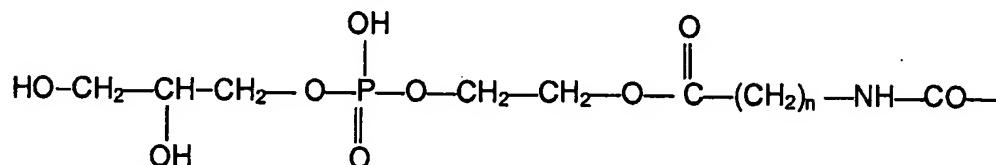
and chemical spacer groups of at least 3 linear carbon atoms, the spacer groups being bonded at their proximal ends to the respective head portion, and at their distal ends to the phosphate of the phospho-glycerol group.

The phospho-glycerol groups forming the end groups of the entities used in this embodiment of the invention have the general formula:



in which R represents C1 - C4 straight chain or branched alkylene, alkylene-oxy, alkylene-thio, alkylene-amine, phenyl, iodo-substituted phenyl, and 5-membered N-heterocyclic groups, with the proviso that they interact with appropriate receptors on antigen-presenting cells.

In a particularly preferred embodiment, the tail portions of the entities such as derivatized beads have the chemical formula:



where n is an integer from 4 – 10, the amide end group being bonded to the head portion surface of the bead.

The term "beads" as used herein is intended to mean substantially any biocompatible body, solid, semisolid or hollow, shape-retaining and typically but not exclusively spheroidal, cylindrical, ellipsoidal including oblate and prolate spheroidal, serpentine, reniform, etc., and from about 50 nanometers to about 500 microns in diameter. They may be flexible or rigid. Preferred materials for their composition are polymethylmethacrylate, polyacrylate, polymethacrylate, glass, polystyrene, polyethylene, polypropylene and the like, of a grade approved for administration to mammalian patients.

The term "physical trauma" refers to trauma physically induced on a mammalian patient which in turn induces an inflammatory response. Such physical trauma includes, wounds, incisions, ischemia (whether induced by exogenous or endogenous factors), etc.

The phospho-glycerol end groups in entities used in this embodiment of the invention may be the distal end group of a phospholipid, namely phosphatidylglycerol, PG, the proximal end of which is attached to a body. These include particles, granules, microspheres or beads of biocompatible

materials, natural or synthetic, such as polyethylene glycol, polyvinylpyrrolidone, polystyrene, etc., polysaccharides such as hydroxethyl starch, hydroxyethylcellulose, agarose and the like, as commonly used in the pharmaceutical industry. Some such suitable substances for derivatization to attach the PG and, in the case of agarose, with PG attached, are commercially available, e.g. from Polysciences, Inc. 400 Valley Road, Warrington, PA 18976, or from Sigma Aldrich Fine Chemicals. The beads may be solid or hollow, or filled with biocompatible material. They are modified as required so that they carry PG molecules on their surfaces.

In a preferred embodiment, such phospho-glycerol carrying entities can be used for administration to patients about to suffer trauma involving wounds, e.g. patients about to undergo surgery or at high risk of suffering a wound as a result of imminent battle action, natural disaster etc., and will precondition the patient's body so as to accelerate the recovery from such subsequently encountered trauma. They will also have the effect of accelerating the recovery of a patient when administered to an already traumatized patient.

A further category of entities for use in another, particularly preferred embodiment of the invention is phosphatidylglycerol (PG) liposomes of the appropriate sizes referred to above, i.e., sizes resembling those of apoptotic mammalian cells or apoptotic bodies, and which have surface PG molecules. As a phospholipid, PG can form the membrane of a liposome, either as the sole constituent of the membrane or as a major or minor component thereof, with other phospholipids and/or membrane forming materials. Liposomes, or lipid vesicles, are sealed sacs, in the micron or sub-micron range, the walls of which consist of layers of suitable amphiphiles. They normally contain an aqueous medium.

The present invention contemplates the use, not only of those liposomes having PG as a membrane constituent, but also liposomes having non-PG membrane substituent but which carry on their external surface molecules of PG, e.g., chemically attached by chemical modification of the liposome surface, making the PG available for subsequent interaction with components of the patient recipient's immune system.

Preferred are liposomes constituted to the extent of 50% - 100% by weight of phosphatidylglycerol (PG), the balance being phosphatidylcholine (PC) or other such biologically acceptable phospholipid(s). More preferred are liposomes constituted by PG to the extent of 65% - 90% by weight. They are prepared from mixtures of the appropriate amounts of phospholipids as starting materials, by known methods.

Methods of preparing liposomes of the appropriate size are known in the art and do not form part of this invention. Reference may be made to various textbooks and literature articles on the subject, for example the review article "Liposomes as Pharmaceutical Dosage Forms" by Yechezkel Barenholz and Daan J. A. Chromeline, and literature cited therein, for example New, R. C., "Liposomes: A Practical Approach," IRL Press at Oxford University Press, Oxford, England (1990), and Nassander, U. K., et al., In: "Biodegradable Polymers as Drug Delivery Systems" (M. Chasin and R. Langer, eds.) Marcel Dekker Inc., New York 1990, pages 261-338.

Such PG-carrying liposomes can be used for administration to patients about to suffer trauma involving wounds, e.g. patients about to undergo surgery or at high risk of suffering a wound as a result of imminent battle action, natural disaster etc., and will precondition the patient's body so

as to accelerate the recovery of such subsequently encountered trauma. They will also have the effect of accelerating the recovery of a patient when administered to an already traumatized patient.

The successful application of the process of the present invention may be manifested in several ways, individually or collectively. The patient may manifest accelerated rate of wound healing, and/or more rapid decline of elevated body temperatures resulting from inflammatory cytokine action and fever as a result of wounding. In addition or in the alternative, the patient may evidence a more rapid recovery of joint mobility, e.g. following orthopedic surgery to replace or to repair a defective body joint (knee, hip, shoulder, etc). A greater survival rate of seriously injured patients is to be anticipated as a result of the use of the present invention. As a result, the duration of the hospital stay for the patient can be significantly reduced.

Another common manifestation of patients obliged to spend long periods in bed as a result of trauma from injury is the development of medical ulcers (decubitus or pressure ulcers). The processes of the present invention are indicated for acceleration of the healing of such ulcers, and indeed for treating and accelerating the healing of mammalian ulcers in general, and thereby further contributing to the shortening of the duration of a patient's hospital stay.

Without being limited by any theory, it is postulated that the sizes of the immune modifying entities used in the invention is such that they will be taken up by cells of the patient's immune system in an apoptosis-mimicking fashion. In general, whatever type of entity is chosen, this means a size from about 50 nanometers to about 500 microns, more preferably from about 50 nanometers to about 500 nanometers.

The entities used in the process of the invention may be administered to the patient by any suitable means which brings them into operative contact with active ingredients of the patient's immune system. Preferably, the entities are constituted into a liquid suspension in a biocompatible liquid such as physiological saline and administered to the patient intra-arterially, intravenously, topically, transdermally (e.g. at a psoriatic site) or most preferably intramuscularly or subcutaneously.

A preferred manner of administering the entities to the patient is as a course of injections, administered daily, several times per week, weekly or monthly to the patient, over a period ranging from a week to several months. The frequency and duration of the course of the administration is likely to vary widely from patient to patient, and according to the severity of the trauma being treated or against which the patient is to be preconditioned. Its design and optimization is well within the skill of the attending physician. A schedule in which a patient receives daily injection on two consecutive days, 10 – 20 days prior to surgery, followed by a single, further injection 1 – 5 dyas prior to surgery, is especially recommended.

The quantities of entities to be administered will vary quite widely depending on the severity of the trauma it is intended to treat or against which is desired to precondition, and on the identity and characteristics of the patient. It is important that the effective amount of entities is non-toxic to the patient, and is not so large as to overwhelm the immune system.

When using intra-arterial, intravenous, subcutaneous or intramuscular administration of a liquid suspension of entities, it is preferred to administer, for each dose, from about 0.1-50 ml of liquid, containing an amount of entities generally equivalent to 1.0% - 1000% of the number of cells normally found in an equivalent volume of whole blood or the number of apoptotic bodies that can be generated from them. Generally, the

number of synthetic entities administered per delivery to a human patient is suitably in the range from about 500 to about 20×10^9 , preferably 10,000 to about 2×10^9 , as indicated by pre-clinical studies. Animal model results may not be truly representative of required numbers on a simple multiple of body weight, in an immune system modifying scenario.

Since the synthetic entities are acting, in the process of the invention, as immune system modifiers, in the nature of a vaccine, the number of such bodies administered to an injection site for each administration is a more meaningful quantitation than the number or weight of synthetic entities per unit of patient body weight. For the same reason, effective amounts or numbers of synthetic entities for small animal use may not directly translate into effective amounts for larger mammals on a weight ratio basis.

The invention is further described, for illustrative purposes, in the following specific examples.

EXAMPLE 1

The invention can be demonstrated by experiments on laboratory rats, pretreating them with a course of injections of phosphatidylglycerol liposomes, surgically inserting temperature and heartbeat measuring probes into the pre-treated animals, and measuring their body temperature and other vital signs using the probes, as a measure of their recovery from the surgical major laparotomy required for insertion. The results are predictive of the effects on other mammals, including humans.

A total of 30 seven week old laboratory bred rats is separated into two groups of 15 animals each: Each animal of the test group A is administered, on day 1, day 2 and day 14 an intragluteal injection of 75% phosphatidylglycerol – 25% phosphatidylcholine liposomes of size 100 ± 20 nanometers, suspended in PBS, of volume 150 μL , each injection

comprising 1,800,000 liposomes. Each animal of the control group B is similarly administered 150 μ L of PBS containing no liposomes, on days 1, 2 and 14.

Four days after the completion of the injections, the animals are anaesthetized, and a telemetry probe is inserted surgically into the femoral artery of each animal. The telemetry probe (DATAQUEST LABPRO, from Data Sciences International) is a commercially available probe equipped with a radio transmitter, to permit heartbeat, systolic blood pressure, diastolic blood pressure and other signals to be received without further handling of the animals. An additional probe is surgically inserted into the peritoneal cavity of each animal, to measure body temperature.

Continuous daily recordings of body temperature, blood pressure and heart rate are made from each animal, for 10 days following the surgery. The group A test animals show a noticeably faster recovery of normal body temperature than the control group B, demonstrating a faster rate of wound healing and recovery from surgery in the test group.

EXAMPLE 2

Surgery on mammalian patients commonly leads to secretion of large amounts of cytokines from the damaged tissue, with consequent weight loss in the patient. The speed with which the patient regains normal body weight is, accordingly, a measure of the rate of recovery from the trauma of surgery.

A group of 10 Balb C adult mice, of stable body weight (the "treatment group") are given intramuscular injections of 75% phosphatidylglycerol – 25% phosphatidylcholine liposomes of size 100 \pm 20 nanometer, suspended in PBS. Each injection has a volume of 50 μ L and

contains approximately 600,000 liposomes. Injection takes place on days 1, 2 and 14. The mice are weighed on each day of injection.

On day 15, each mouse is subjected to laparotomy, and the wounds promptly stitched. The mice are weighed immediately 20 minutes after being stitched, and every 24 hours thereafter, for 7 days. Another group of 10 similar mice (the "control group") are similarly weighed, subjected to laparotomy, wound stitching and weighing on the same schedule, but receive no injection of liposomes.

A noticeable and significant increase in the rate at which the treatment group of mice recover their pre-operative body weight, as compared with the control group, is apparent.

All patents, patent applications, and publications previously cited above are herein incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. Use in preparation of a medicament for treating a mammalian patient suffering from physical trauma, or treating a mammalian patient at risk of suffering such trauma to lessen the severity of and/or accelerate the recovery from such trauma, of immune system-modifying entities, each comprising a body of a size similar to an apoptotic mammalian cell or apoptotic body, and having exposed on its surface phospho-glycerol groups, the entities being capable of modulating the patient's immune system with accompanying beneficial effects including inhibition of pro-inflammatory cytokines and/or promotion of anti-inflammatory cytokines.

2. Use according to claim 1 wherein the entities are synthetic beads carrying phospho-glycerol groups.

3. Use according to claim 1 wherein said entities are PG liposomes.

4. Use according to claim 3 wherein the PG liposomes comprise from 50% to 100% PG by weight.

5. Use according to any preceding claim wherein the bodies have a diameter of from 50 nanometers to 500 microns.

6. Use according to any preceding claim wherein the unit dose is from about 500 to about 20×10^9 entities.

7. A process of treating a mammalian patient suffering from physical trauma, or treating a mammalian patient at risk of suffering such trauma (by

surgical treatment, or by suffering unanticipated accidental injuries, battle injuries or the like) to lessen the severity of and/or accelerate the recovery from such trauma, which comprises administering to the patient an effective immune system modifying amount of immune system-modifying entities, each comprising a body of a size similar to an apoptotic mammalian cell or apoptotic body, and having exposed on its surface phospho-glycerol groups, the entities being capable of being taken up by cells of the patient's immune system with accompanying beneficial effects including inhibition of pro-inflammatory cytokines and/or promotion of anti-inflammatory cytokines.

8. The process of claim 7 wherein said entities are phosphatidylglycerol liposomes.
9. The process of claim 7 wherein the phosphatidylglycerol liposomes have a size from 50 nanometers to 500 microns.
10. The process according to claim 7 wherein the entities are synthetic beads carrying phospho-glycerol groups.
11. The process according to claim 8 wherein the PG liposomes comprise from 50% to 100% PG by weight.
12. The process according to any of claim 10, 11, 12 or 13 wherein the bodies have a diameter of from 50 nanometers to 500 microns.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 03/01407

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/127 A61K31/683 A61K9/16 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 34270 A (HILLS BRIAN ANDREW ;BRITANNIA PHARMACEUTICALS LTD (GB); WOODCOCK D) 2 May 2002 (2002-05-02) the whole document	1,5-7
Y	WO 90 11781 A (ALCON LAB INC) 18 October 1990 (1990-10-18) the whole document	2,10,11
X	WO 98 53800 A (APPLIED BIOTECHNOLOGY INC ;KOROLY MICHAEL V (US)) 3 December 1998 (1998-12-03) page 1, line 15-29	1,3,5-9, 12
Y	WO 98 53800 A (APPLIED BIOTECHNOLOGY INC ;KOROLY MICHAEL V (US)) 3 December 1998 (1998-12-03) page 4, line 24 -page 6, line 4 page 9, line 4-13; claims 1,5,6,14	2,10,11
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the International search report
3 February 2004	13/02/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patenttaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Greif, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 03/01407

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AR'RAJAB A ET AL: "Exogenous phospholipid reduces postoperative peritoneal adhesions in rats" EUROPEAN JOURNAL OF SURGERY, STOCKHOLM, SE, vol. 161, no. 5, 1995, pages 341-344, XP002090689 ISSN: 1102-4151 abstract page 314 ---	1-12
Y	EP 0 299 937 A (BENGMARK STIG ;LARSSON KARE (SE)) 18 January 1989 (1989-01-18) column 1, line 33-57 column 5, line 13-16 ---	1-12
Y	US 5 670 631 A (BAYERL THOMAS ET AL) 23 September 1997 (1997-09-23) abstract figures 1,2 ---	2,10
A	US 5 770 234 A (GIRIDHAR GIRISH ET AL) 23 June 1998 (1998-06-23) the whole document ---	1-12
A	EP 0 516 034 A (FIDIA SPA) 2 December 1992 (1992-12-02) the whole document ---	1-12

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,5,6,7,10,12 (all in parts)

Present claims 1,2,5,6,7,10 and 12 relate to a use or process of treating defined by reference to a desirable characteristic or property, namely

"immune-modifying entities, each comprising a body of a size similar to an apoptotic mammalian cells or ooptotic body, and having exposed on its surface phospho-glycerol groups, the entities being capable of modulating the patient's immune system with accompanying beneficial effects including inhibition of pro-inflammatory cytokines and / or promotion of anti-inflammatory cytokines".

The claims cover all uses and processes of treatint having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such uses or processes of treating.

Furthermore, an attempt is made to define the use of process of treating by reference to a result to be achieved, i.e. the inhibition of pro-inflammatory cytokines and /or the promotion of anti-inflammatory cytokines".

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT).

This lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the uses or processes of treating as defined in claims 3, 4, 8, 9, and 11, as well as the examples 1 and 2 in the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/01407

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1,2,5,6,7,10,12 (all in parts) because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 03/01407

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